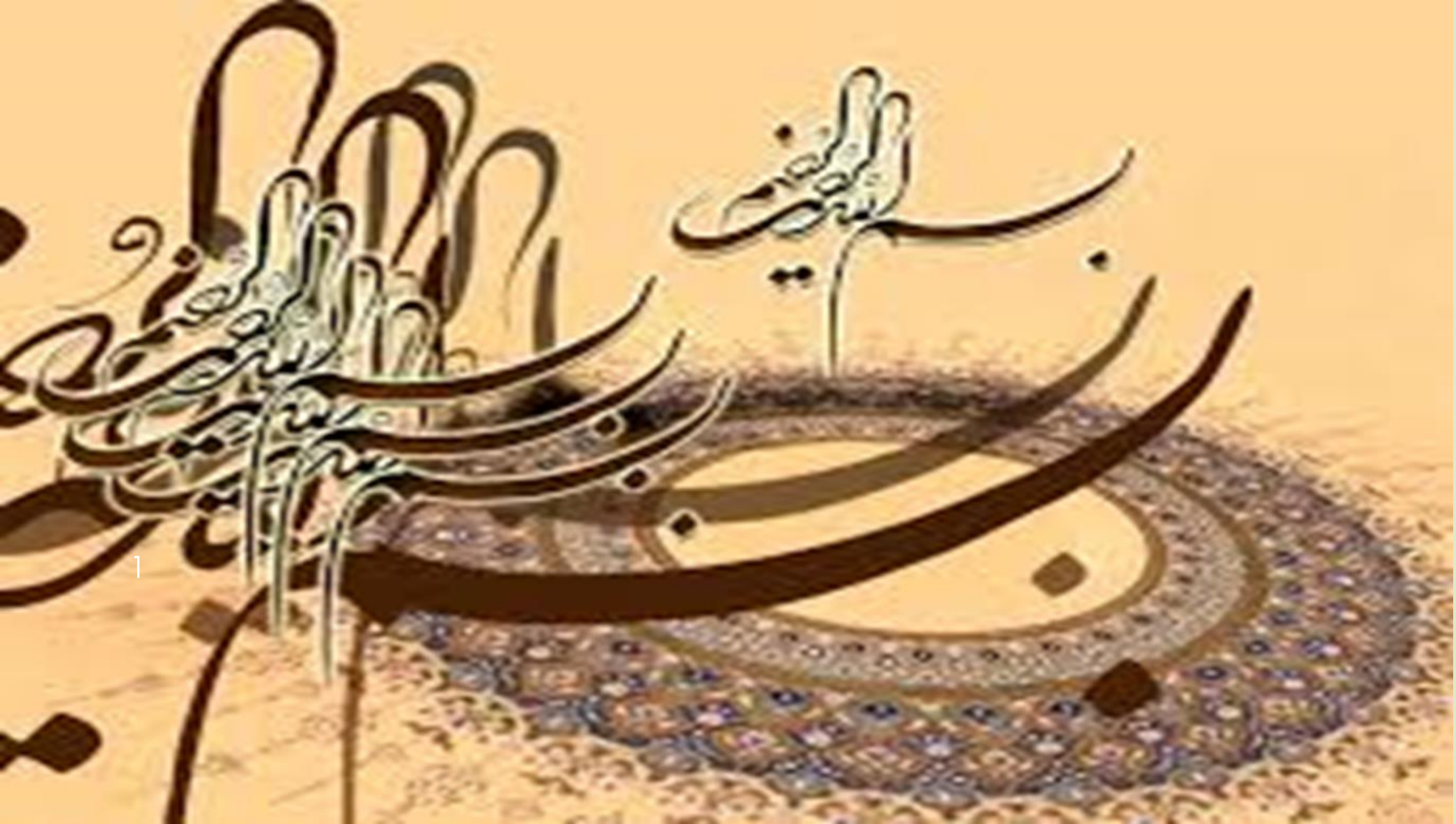

بسم الله الرحمن الرحیم

Crosslinking & biopolymers in tissue engineering

Presented by: Navaeian.M

Under supervision of Dr. Ahmadpour

Medical biotechnology

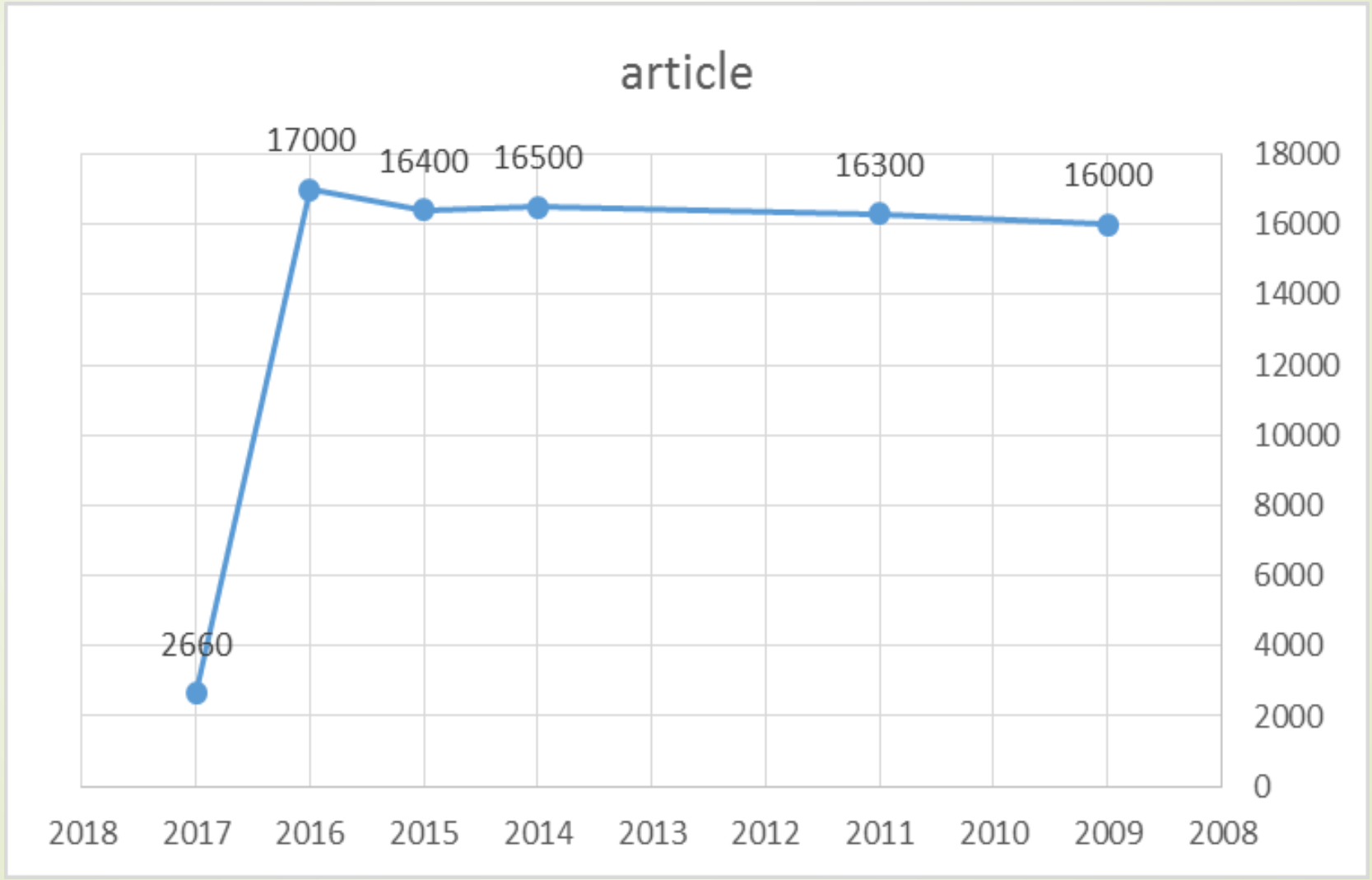
Qazvin university of medical science

CONTENTS

CONTENTS…

Introduction

Crosslinking & biopolymers in tissue engineering /2008 to 2o17



Google scholar

➢Last updated:04/05/2017

Introduction

Review

CellPress

Crosslinking biopolymers for biomedical applications

Narendra Reddy[1], Roopa Reddy[1], and Qiuran Jiang[2,3]

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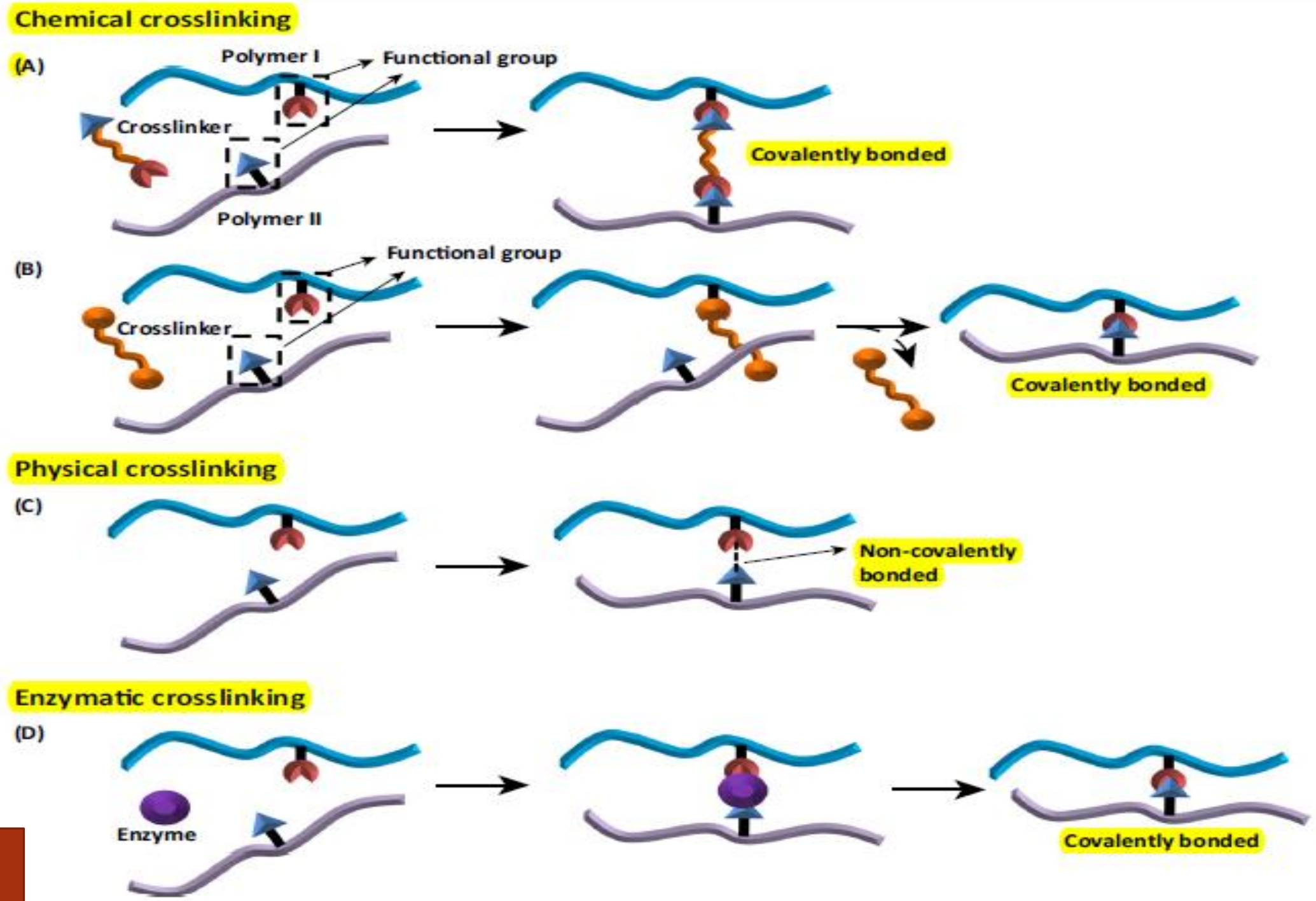
[3] Department of Technical Textiles, College of Textiles, Donghua University, Shanghai, P.R. China

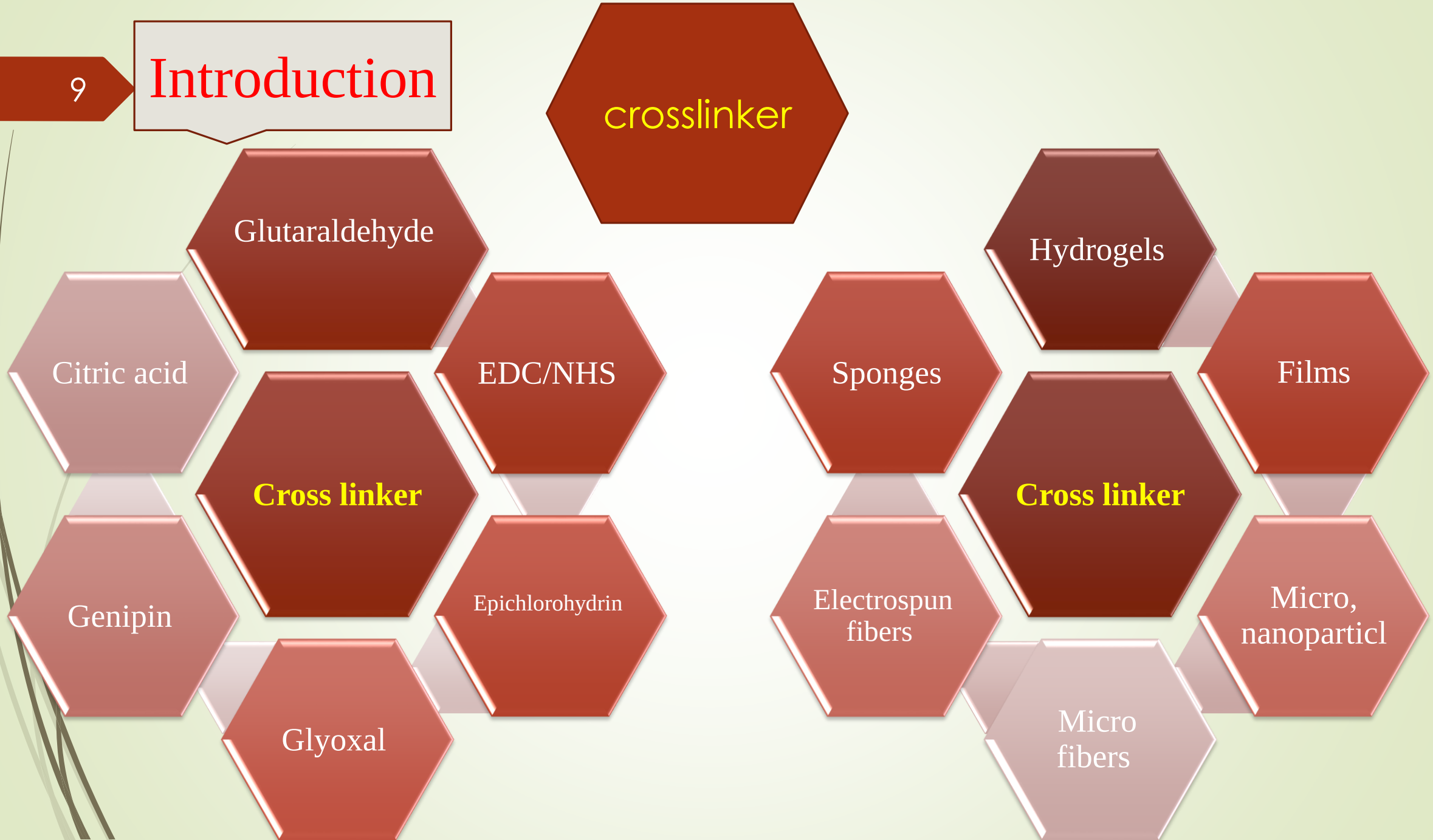
Biomaterials made from proteins, polysaccharides, and synthetic biopolymers are preferred but lack the mechanical properties and stability in aqueous environments necessary for medical applications. Crosslinking improves the properties of the biomaterials, but most crosslinkers either cause undesirable changes to the functionality of the biopolymers or result in cytotoxicity.

and in many instances the stability in aqueous and physiological environments required for medical applications [6]. For instance, films and electrospun structures made from proteins disintegrate at high humidities or in aqueous solutions [7,8]. Crosslinking has been the most common approach to overcome the limitations of biomaterials [9,10]. Crosslinkers interconnect molecules, increase mo-

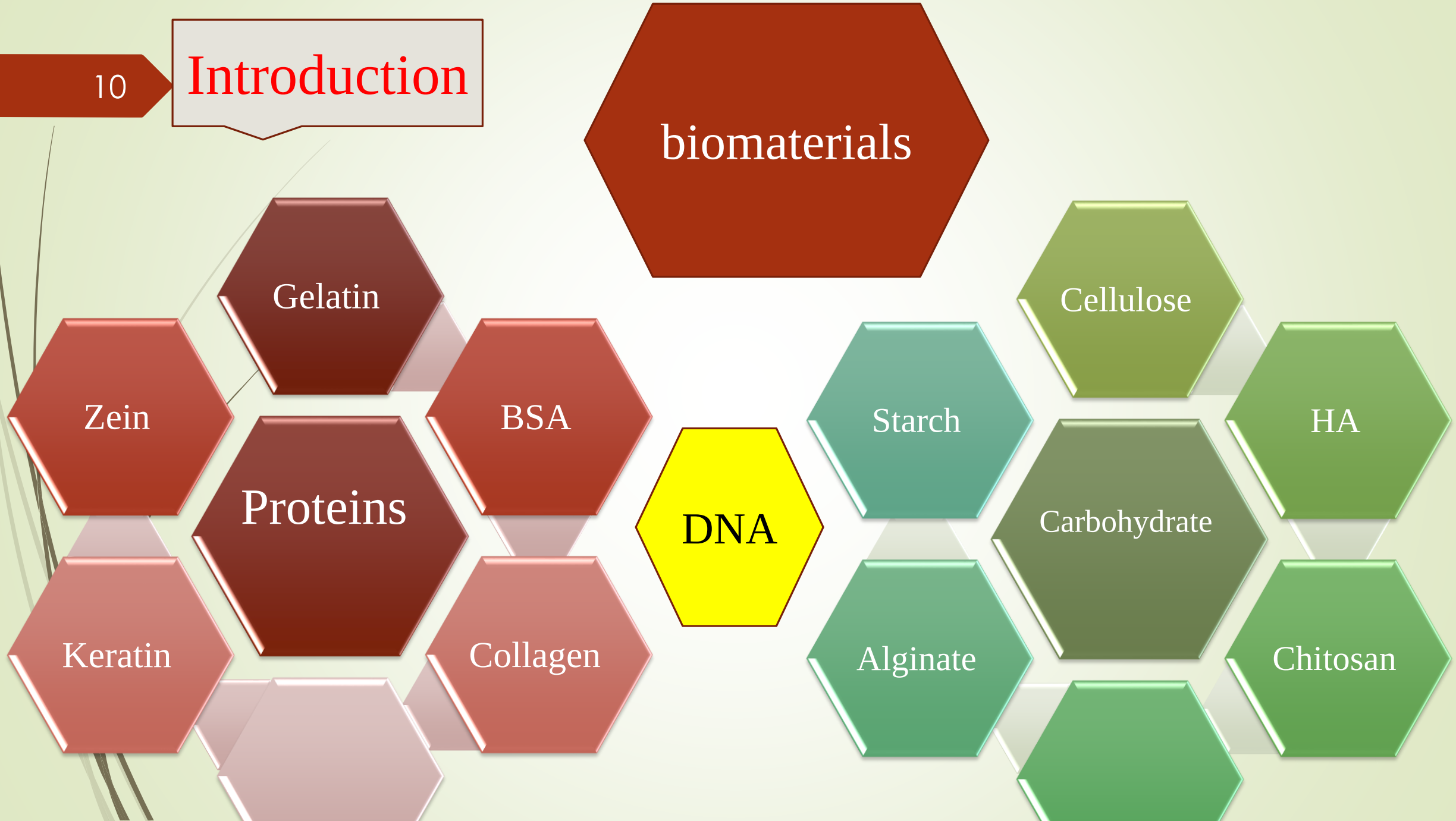
methods of crosslinking



Introduction



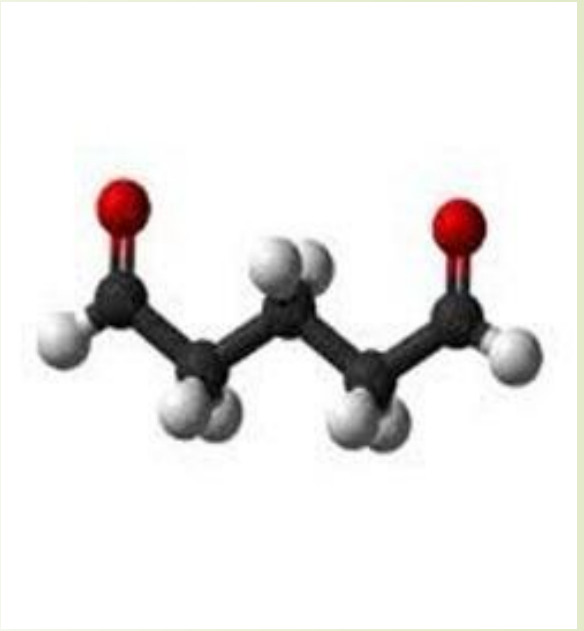
Introduction



Discussion

Discussion

Glutaraldehyde

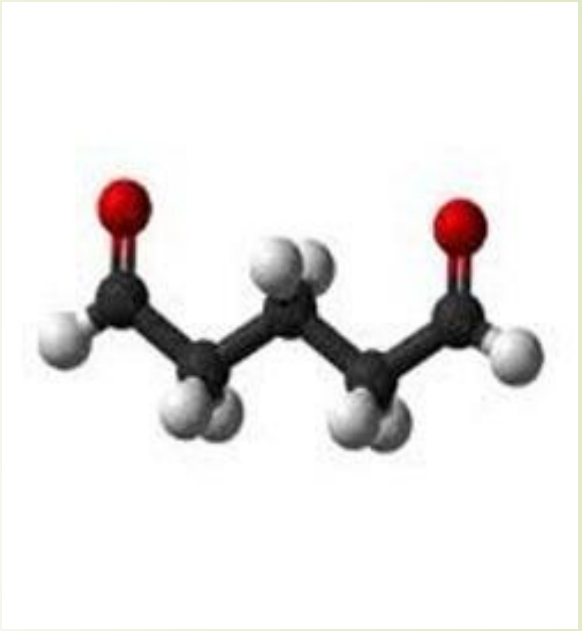


Advantage

- functional groups whit proteins & carbohydrates(1)
- improvement in tensile properties(1)
- improvement in mechanical properties (1)
- accelerate the calcification(9)

Discussion

Glutaraldehyde



Advantage

- flexible & transparent (10)
- in many application biodegradable (5)
- a low cost cross linker

Discussion

Glutaraldehyde

Disadvantage

- Cytotoxicity(non-cytotoxic : up to 8%)(1)

Discussion

carboxylic acids

- crosslink both polysaccharides and proteins
- biocompatible
- 2 carboxylic groups can crosslink biopolymer in wet and dry conditions
- fibers, fils, electrospun crosslinked with citric acid.(1)

Discussion

carboxylic acids…

- Crosslinked in dry & wet condition
- Improvement in tensile properties
- ↑ stability under aqueous condition(1)

Contents lists available at ScienceDirect

Carbohydrate Polymers

journal homepage: www.elsevier.com/locate/carbpol

Citric acid crosslinked β-cyclodextrin/carboxymethylcellulose hydrogel films for controlled delivery of poorly soluble drugs

Vishwajeet Sampatrao Ghorpade[a,*], Adhikrao Vyankatrao Yadav[b], Remeth Jacky Dias[a]

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ARTICLE INFO

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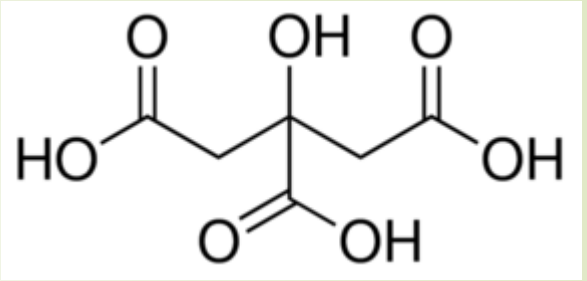
ABSTRACT

Citric acid crosslinked β-cyclodextrin–carboxymethylcellulose (βCD-CMC) hydrogel films were prepare
by esterification–crosslinking method for the controlled release of ketoconazole (model drug). The hydro

Discussion

Citric acid

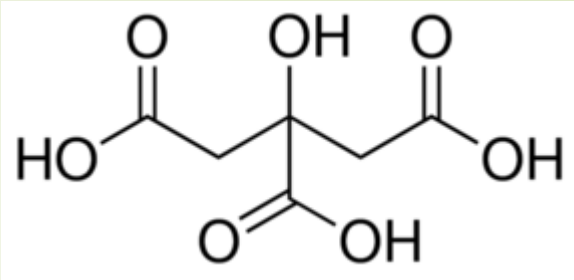


Advantage

- improve the mechanical properties (1)
- stability of biomaterials (1)
- Provides pendant functionality (1)
- formation of ester bonds → better compatibility(1)

Discussion

Citric acid …

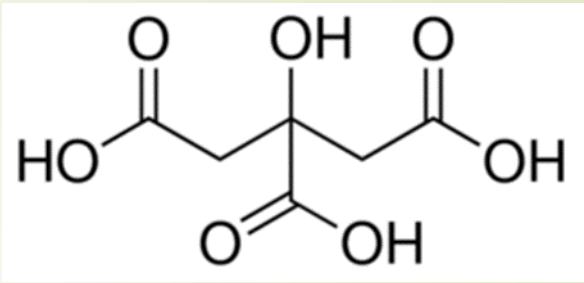


Advantage

- Up to the 80% of **citric acid** in the human body is found in bones
- good tensile properties
- Water stability

Discussion

Citric acid…

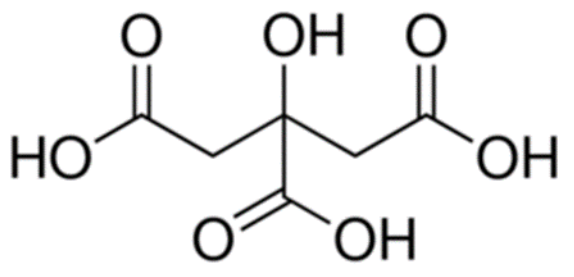


Advantage…

- Successfully used as a cross linker
- cheap
- non-toxic(6)

Discussion

Citric acid…

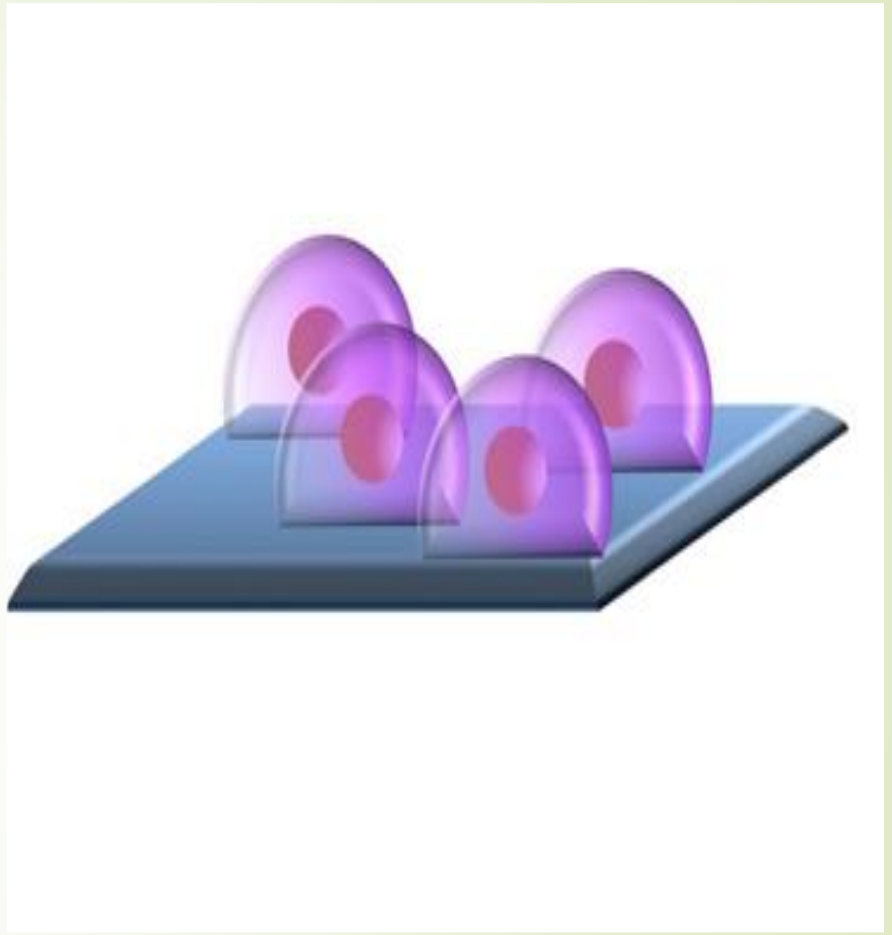


- Decreased crosslinking using 10% ≠ using lower **citric acid**

the fibers were crosslinked with **citric acid** to improve tensile properties and water stability

Discussion

Films



Advantage

- Easiest biomaterial to be fabricated (1)
- controlled release (1)
- Poor dissolve in water

Discussion

Films & EDC/NHS

- ↑ tensile strength
- improvement in mechanical properties
- aqueous stability (1)

EDC/NHS : N-Ethyl-N0-(3-(Dimethylamino)propyl)Carbodiimide/N-Hydroxyl Succinimide

Discussion

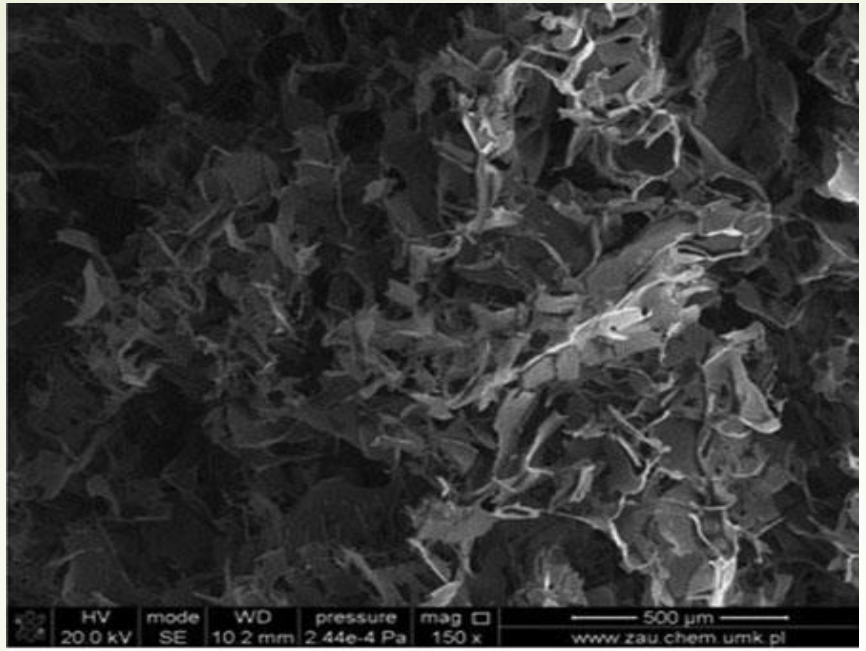
EDC/NHS+…

- Mechanical properties were improved
-  Tensile properties
- better stability in water(13)

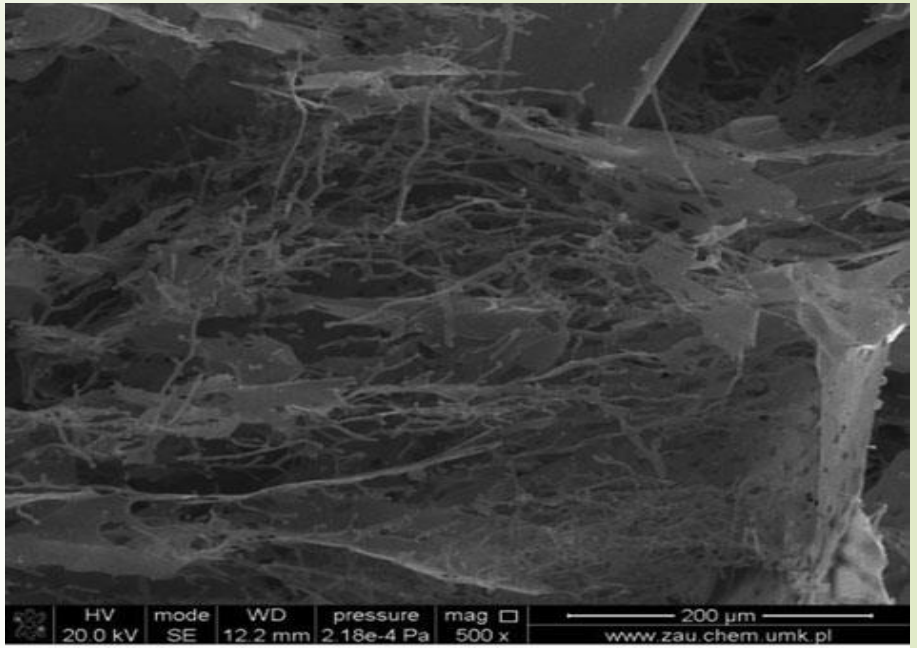
25

a)Non-cross-linked

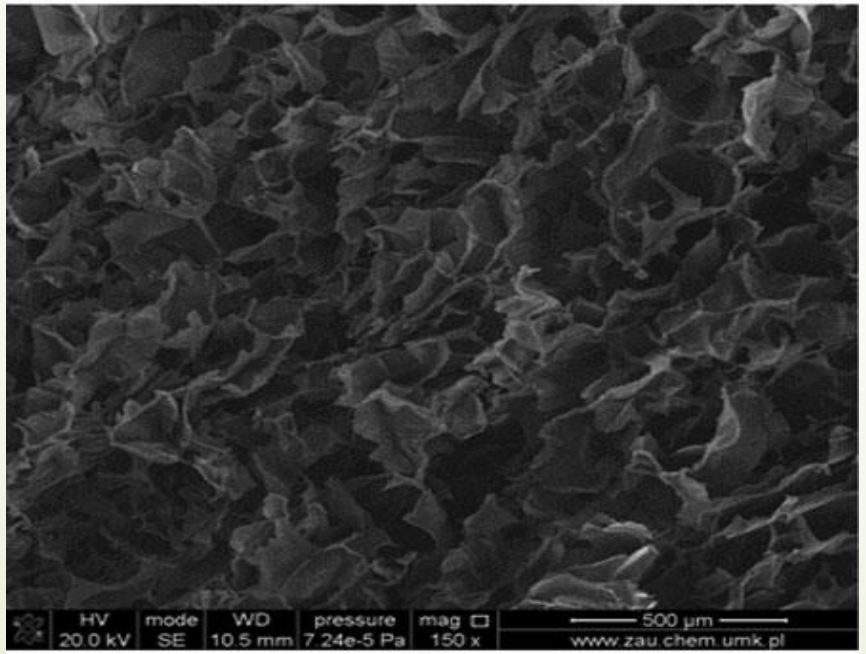
b) Cross-linked with EDC/NHS



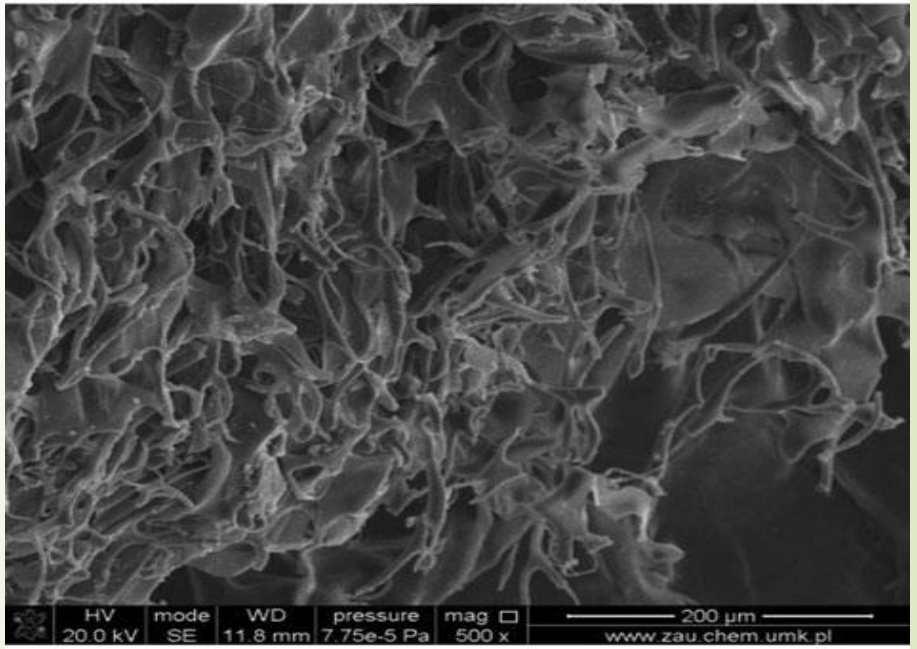
(a)



(a)



(b)



(b)

13

Discussion

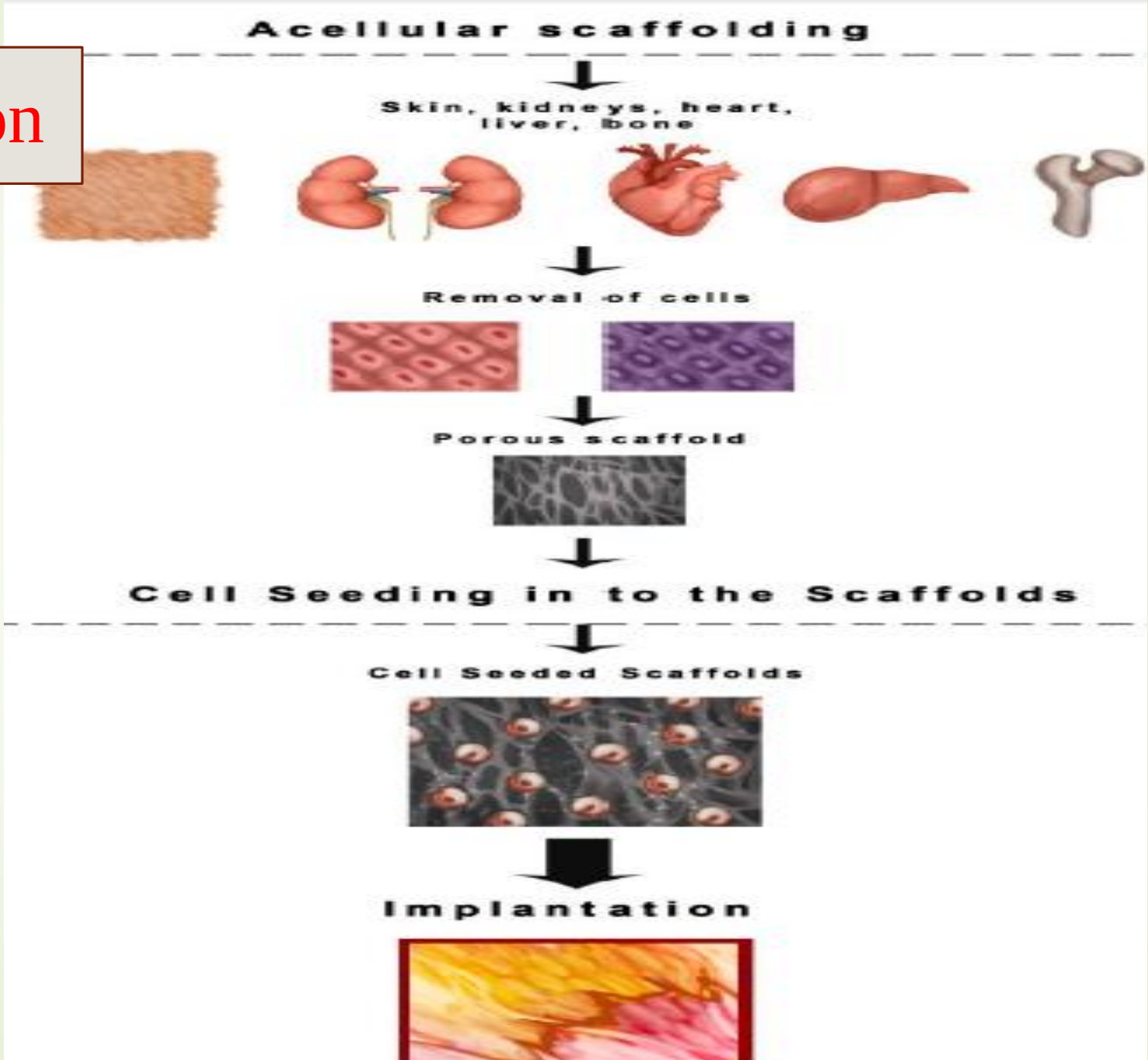
EDC/NHS+…

- **Carbodiimide** crosslinking whit:
  - Type A gelatin
  - Type B gelatin
  - Collagen

- Amide bond found in **carbodiimide**-cross-linked product.

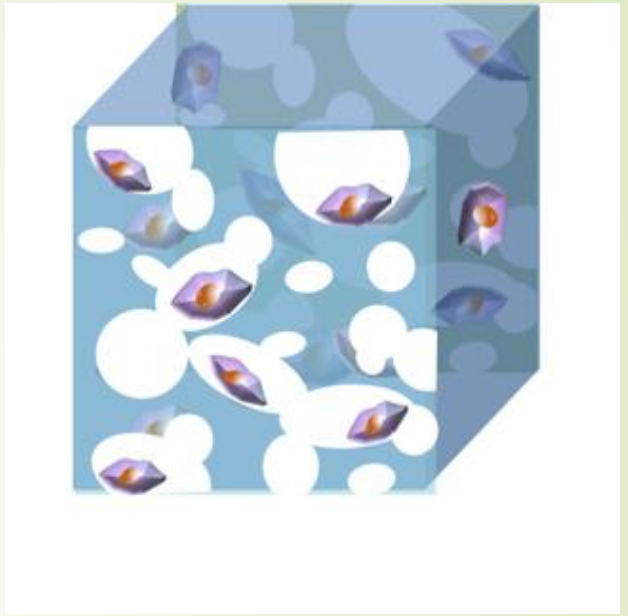
Discussion

Scaffold:
sponge & fibres ….



Discussion

Sponges



- 3D porous structures
- used as scaffolds for culturing of osteoblasts
- tooth tissue engineering

Discussion

Sponges…

Disadvantage

- Poor mechanical properties
- Poor stability in water

Discussion

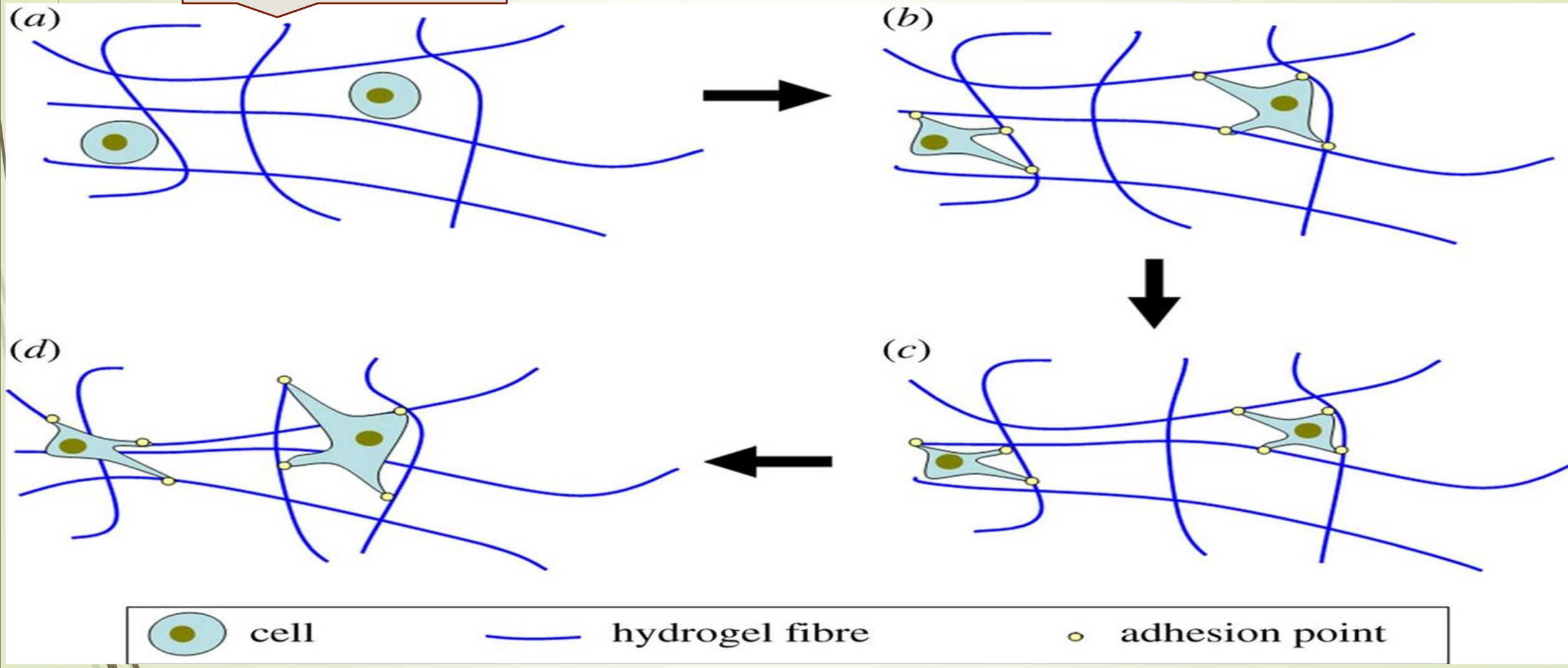
Sponges & EDC/NHS

- Sponges ✚ EDC/NHS ✚ lysine ✚ glutamic acid ✚

glycine ➡ improved thermal stability & lower rate of biodegradation

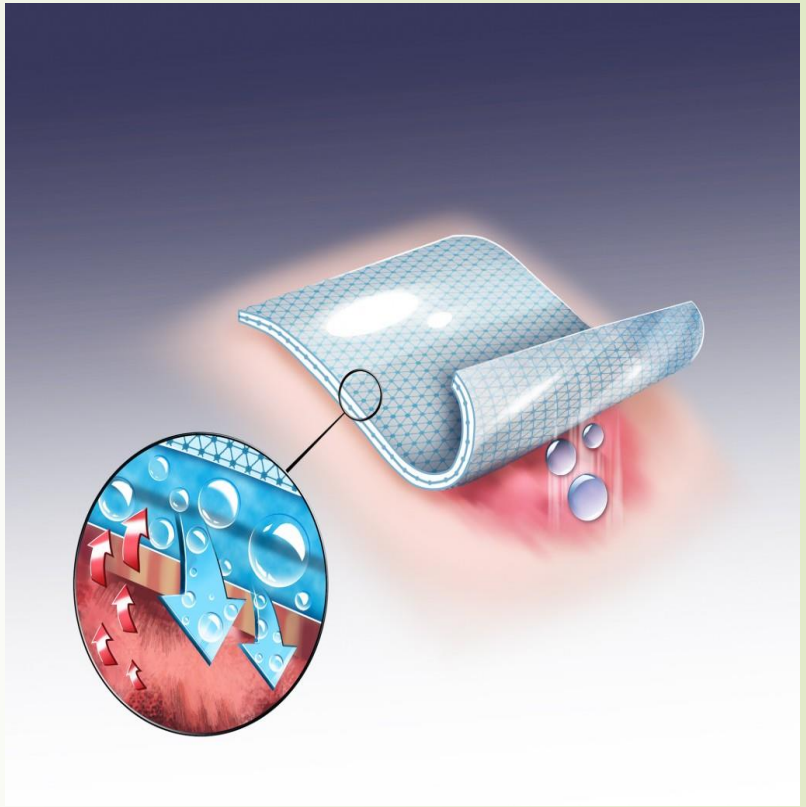
Discussion

Hydrogel



Discussion

Hydrogel



Advantage

- capacity to retain large amounts of water(1)
- Delivery of drugs, peptides, and proteins(1)
- usable for in vitro and in vivo applications (1)
- high swelling &maintain morphology → useful for ophthalmic, wound healing(1)

Discussion

Hydrogel Wound Dressing

The Japan Science and Technology Corporation contracts research on this material to the private sector.

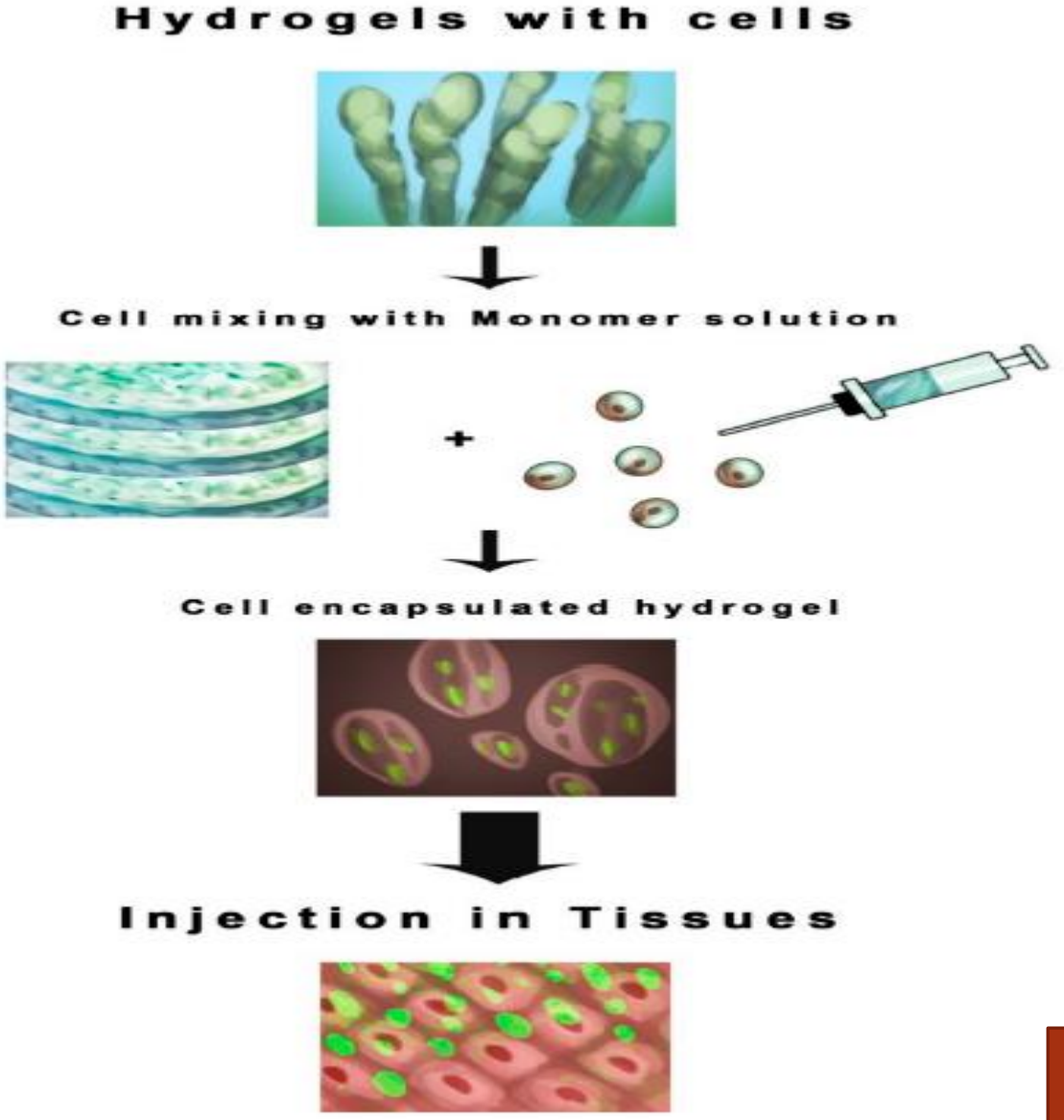
Merits
1. Speeds healing
2. Painless removal of the dressing
3. No residue
4. Transparency enables observing the healing process

Product

Example of treatment

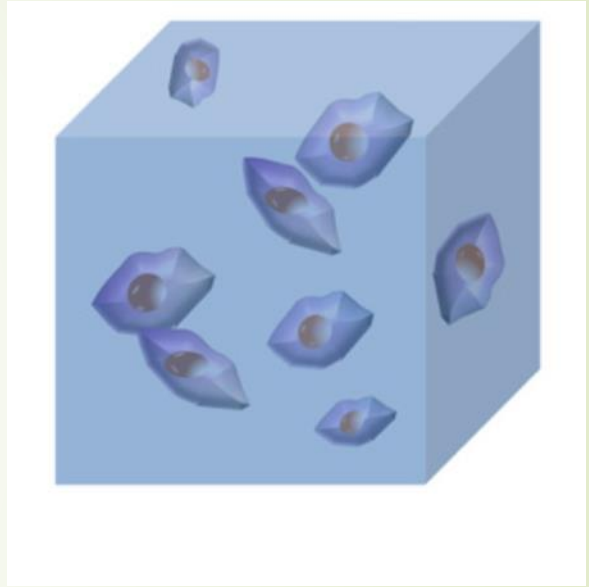
Use: ①Skin burns ②Bedsores ③Pharmaceutical chemical for wet cloth ④Facial pac

Hydrogel…



Discussion

Hydrogel…



- **Advantage….**
- Called “smarts materials”(4)
- highly porous structure(6)
- Composed of natural polymers
- Can enhance specific cellular functions
- excellent biological functions
- maintain cell viability

Discussion

Hydrogel…

➢Drug delivery

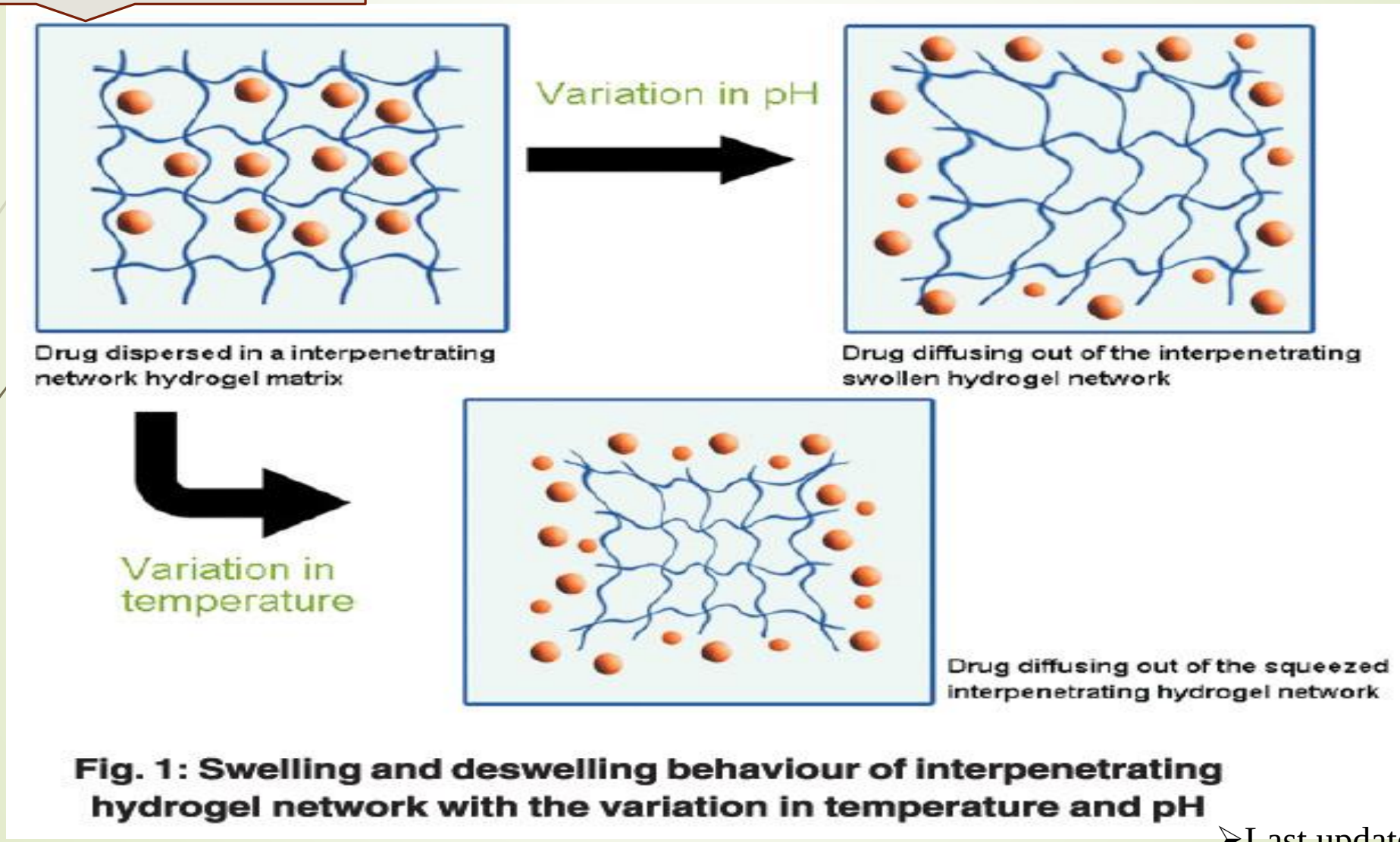


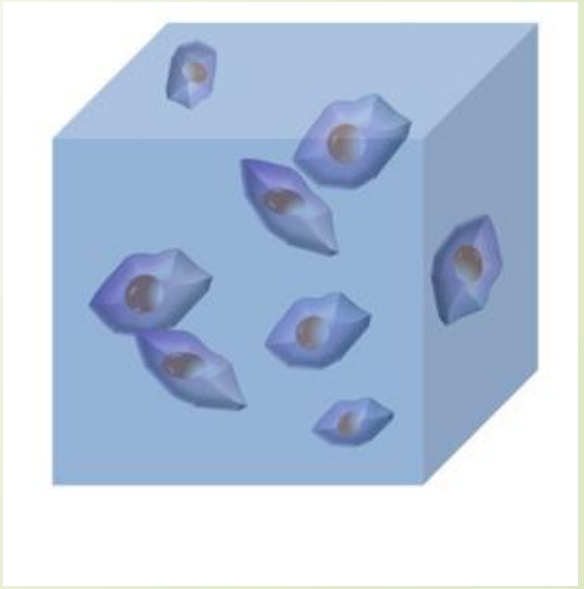
Fig. 1: Swelling and deswelling behaviour of interpenetrating hydrogel network with the variation in temperature and pH

Discussion

Hydrogel

Advantage….

- ability to swell in water without getting dissolved in it(6)



Int

Hydrogels are hydrophilic, 3D-crosslinked polymeric network and superabsorbent when placed in water or other physiological fluids due to their swelling ability [1]. Crosslinking in hydrogels occurred through physical interactions or covalent bonding. Hydrophilic groups like —OH, —NH_2, —COOH, etc. are responsible to generate hydrophilicity in hydrogels. In swollen form due to their softness and rubber like structure, hydrogels appear like a living tissue. Hydrogels are prone to sense a minor change in external stimuli like (pH, temperature, ionic concentration, electric and magnetic field) by displaying variation in swelling response, mechanical properties and network structure [2].

pH-responsive smart hydrogels are one of the most premium type of hydrogels that has been widely used in medicine for controlled/targeted drug release. The significance of pH-responsive hydrogels is due to their performance in different pH of internal

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bones of such polymers. These pendant ionic groups are responsible for the pH-sensitivity of the hydrogels. Hydrogels based on natural/biopolymers are ecofriendly, biodegradable, biocompatible, nontoxic, superabsorbent, hydrophilic, cost effective and have ability to expand making it favorable to be used in biomedical, cosmetics, biotechnology mainly for drug delivery and agricultural applications [4–6].

Among biopolymers, the polysaccharides (cellulose, agar, pectin, carrageenan and alginic acid) are the most abundant and renewable natural polymers and are neutral or acidic in nature. Chitosan is a cationic biopolymer acquired through the alkaline *N*-deacetylation of naturally occurring chitin. Chitin is an important constituent of crustaceans, insects and fungal mycelia consists of 2-acetamido-2-deoxy-β-D-glucose attached through a β (1,4) linkage [7]. Glucosamine are the major units in chitosan having one primary amino and two free hydroxyl groups [8]. The degree of *N*-deacetylation is the main factor which decides its properties [9]. Chitosan is a biocompatible [10], biodegradable [11], antifungal, antibacterial [12] and having gel forming properties [13], so, read-

Development of a novel pH sensitive silane crosslinked injectable hydrogel for controlled release of neomycin sulfate

Sehrish Jabeen[a,b], Atif Islam[b,*], Abdul Ghaffar[a,b], Nafisa Gull[b], Ayesha Hameed[b], Anbreen Bashir[a,b], Tahir Jamil[b], Tousif Hussain[c]

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ABSTRACT

Silane crosslinked biopolymer based novel pH-responsive hydrogels were fabricated by blending the cationic (chitosan) and anionic (alginate) polymers with poly(vinyl alcohol). Tetraethoxysilane (TEOS) was used as a crosslinker in different amounts due to its nonhazardous nature, to study its impact on

Discussion

Hydrogel…

- **Advantage….**
- Hydrophilic
- Superabsorbent
- Appear like a living tissue.
- Are prone to sense a minor change in external stimuli(7)

Discussion

Hydrogel…

Advantage….

- Better growth of cancer cells in the gelatin **hydrogels**
- Cells were successfully encapsulate

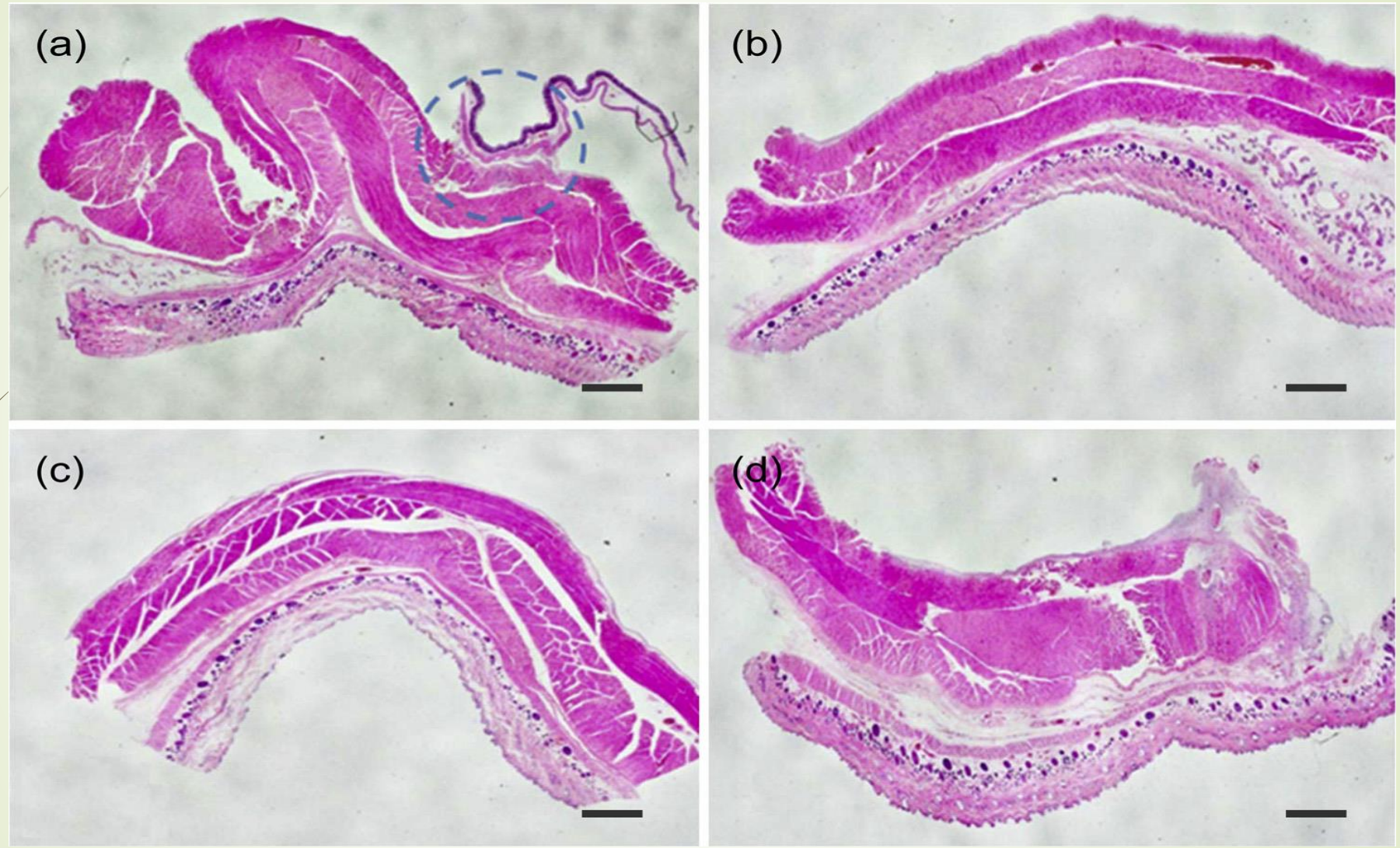
Discussion

Hydrogel…

- Ecofriendly, biodegradable, biocompatible
- Nontoxic
- Cost effective

- To be used in:
- Biomedical , cosmetics, biotechnology mainly for drug delivery and agricultural applications(7)

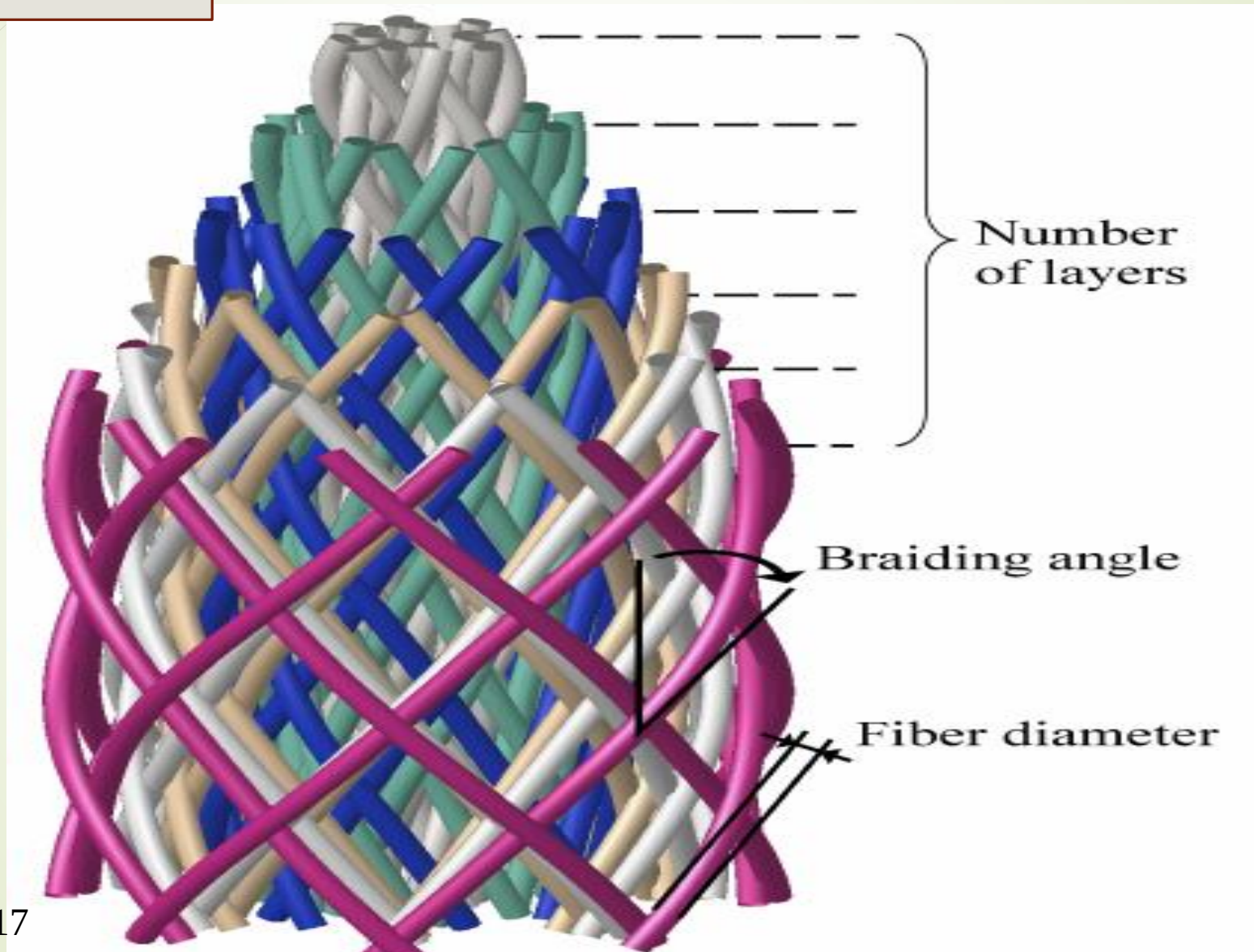
Hydrogel…



Histological observation of abdominal walls treated with modified hydrogel at 14 days after surgery

Discussion

fibers



Discussion

fibers

- as sutures & tissue engineering scaffolds
- made fibers : collagen, &wheat & gluten & soy proteins

use as:

- tissue engineering
- drug delivery
- Scaffolds(1)

Discussion fibers

Advantage

- good mechanical properties under dry conditions

Disadvantage

- poor stability under aqueous conditions

Discussion

fibers

- fibers ✚ gelatin ✚ genipin ⟶ delivery of NGF

- considered ideal for regeneration of nerve(1)

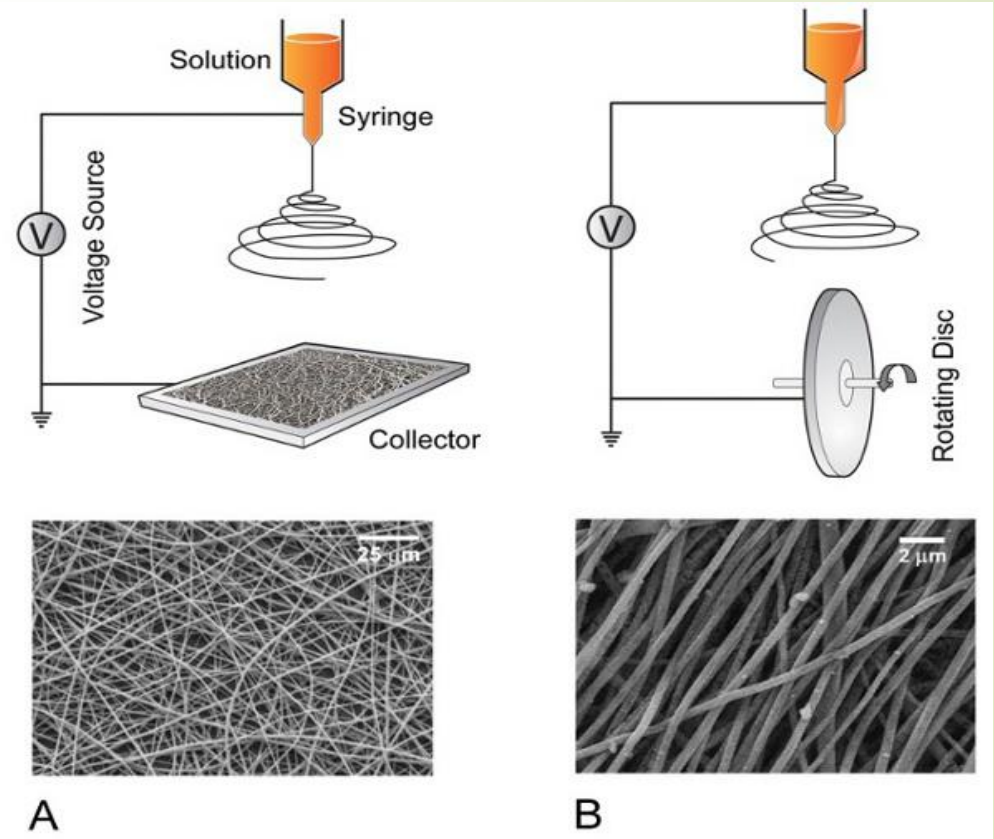
NGF=Nerve Growth Factor

Discussion

Electrospun fibers

- Made of: biopolymers resemble the ultrafine fibrous network in ECM
- can promote the attachment
- Proliferation of cells(1)

ECM=Extracellular Matrix

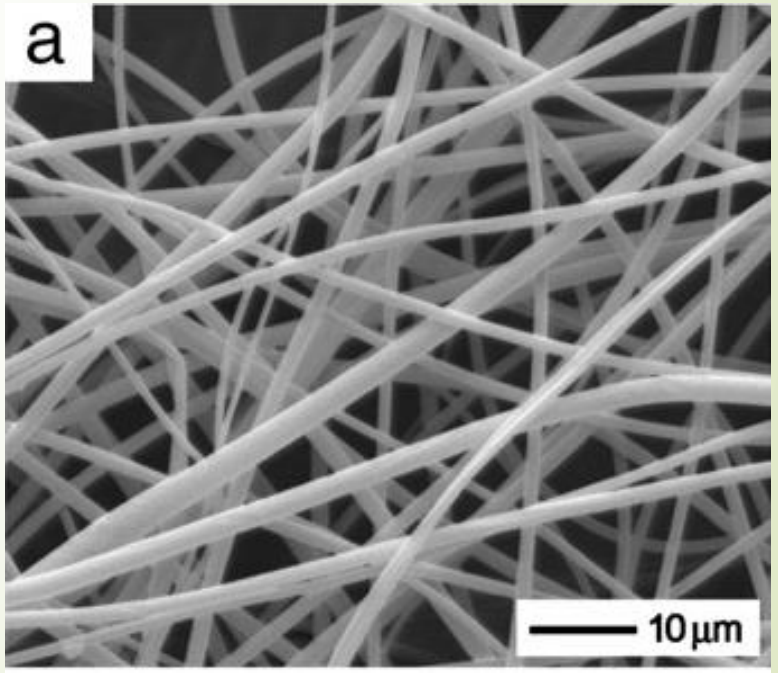


- Last updated:04/05/2017

Discussion

Electrospun fibers…

- mechanical properties similar to of native tissue



Disadvantage

- poor water stability

Discussion

Electrospun fibers…

electrospun fibers ✚ saturated glutaraldehyde vapor ➡

- ⬆ tensile strength
- resist collagenase

- ⬇ Porosity
- Cytotoxicity
- citric acid ✚ electrospun collagen fibers ✚ glycerol

Discussion

Electrospun fibers…

electrospun fibers + zein →

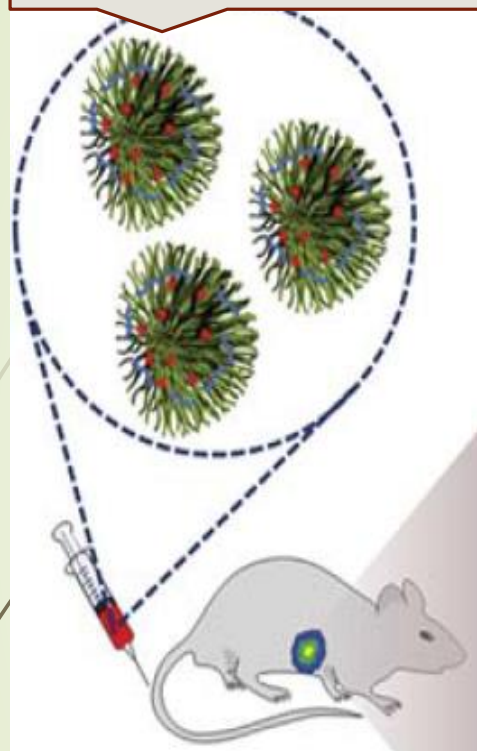
- weak tensile propertie
- rapidly dissolve in aqueous solutions

electrospun fibers + zein + citric acid →

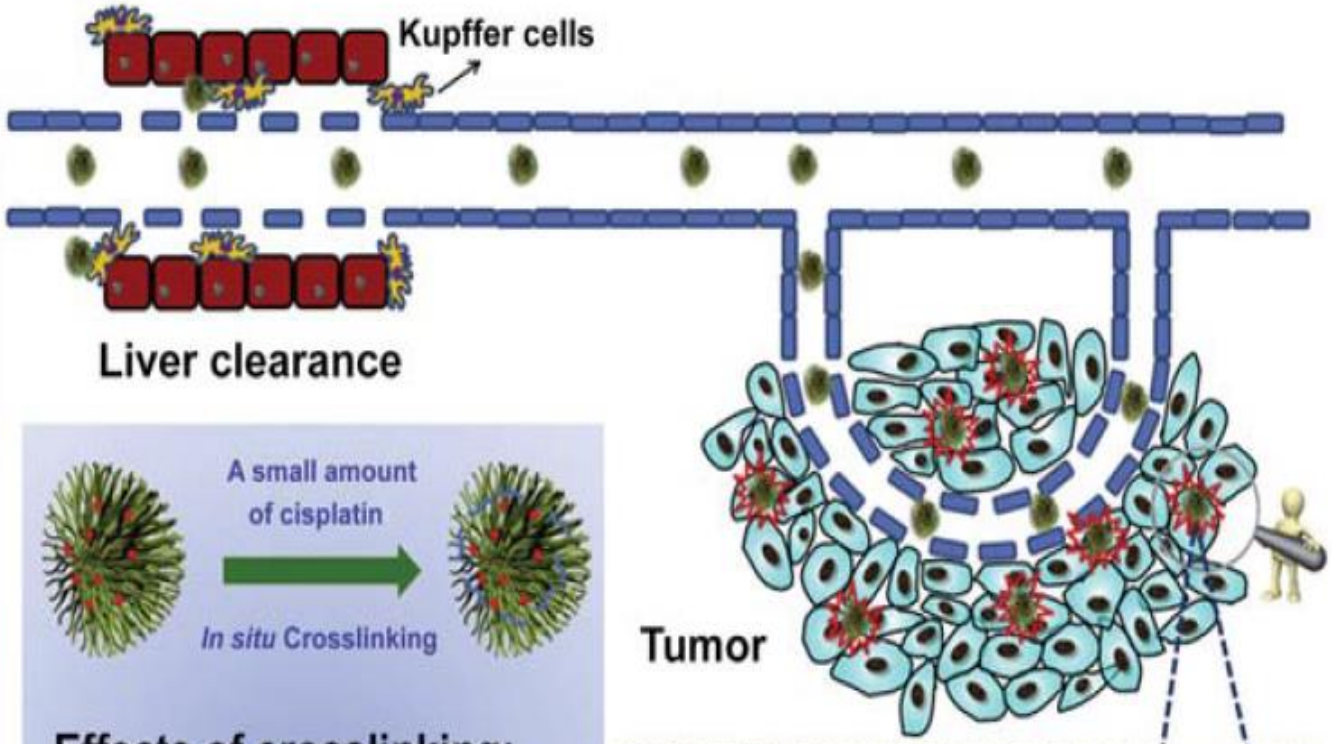
- attachment
- proliferation of fibroblasts(1)

Discussion

micro- and nanoparticles

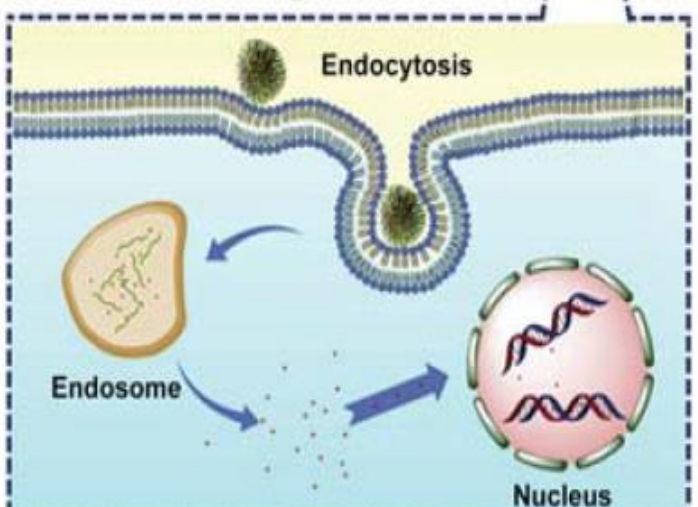


Mice xenograft model of human NSCLC



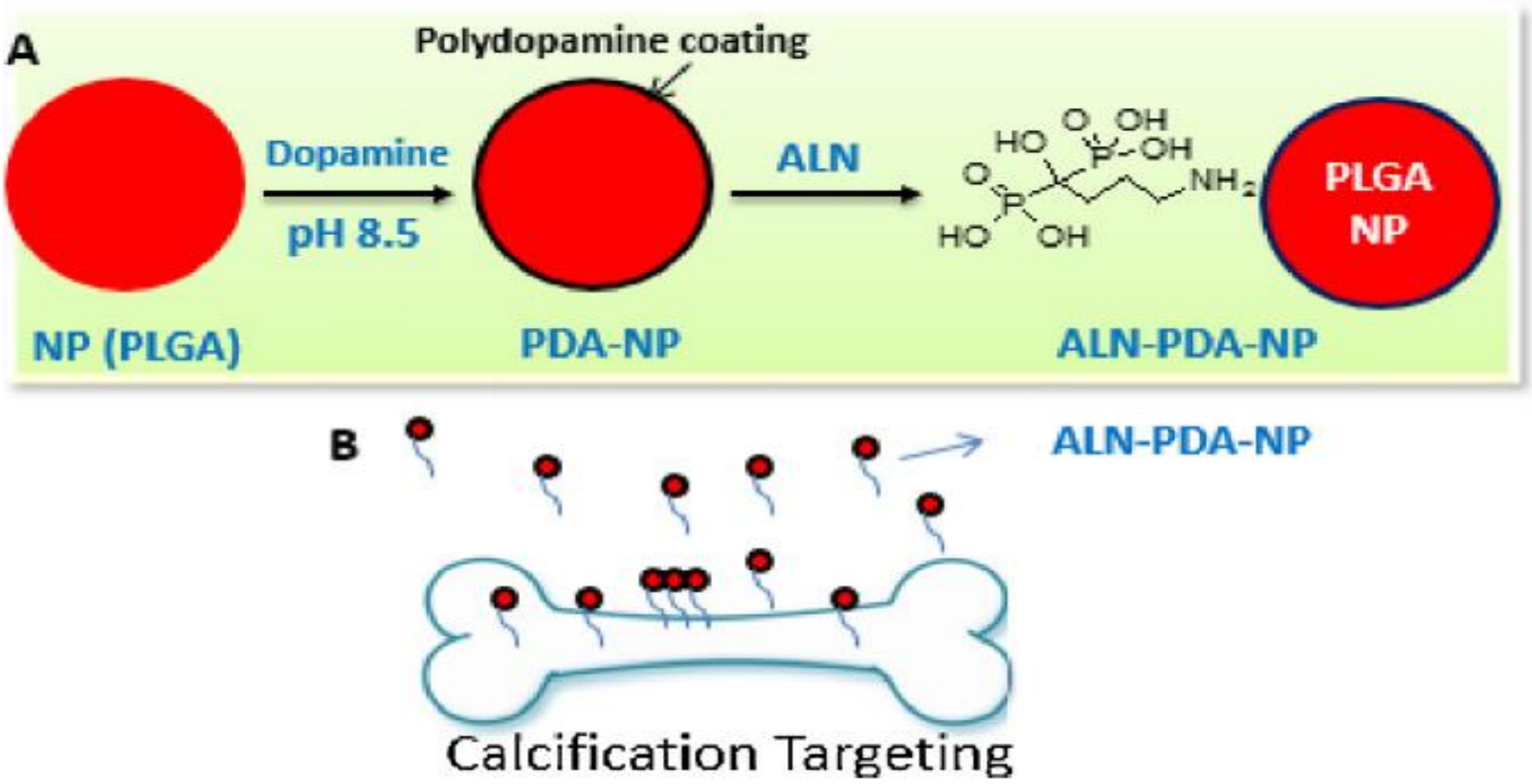
Effects of crosslinking:

- Reinforced stability and delayed drug release;
- Prolonged blood circulation;
- Improved safety and tolerability;
- Optimized biodistribution;
- Reduced systemic toxicity;
- Enhanced antitumor efficacy.



Discussion

micro- and nanoparticles



Discussion micro- and nanoparticles

- in vivo delivery of drugs
- biopolymers & metallic & synthetic polymers

Limitation biopolymers :

- Poor stability
- agglomeration
- ⬆ particle size
- relatively quick degradation(1)

Discussion micro- and nanoparticles…

- Chitosan nanoparticles → control release of drugs

protein nanoparticles :

- unstable under physiological environment
- accumulate in the kidneys(1)

Discussion

Biomaterial

Discussion

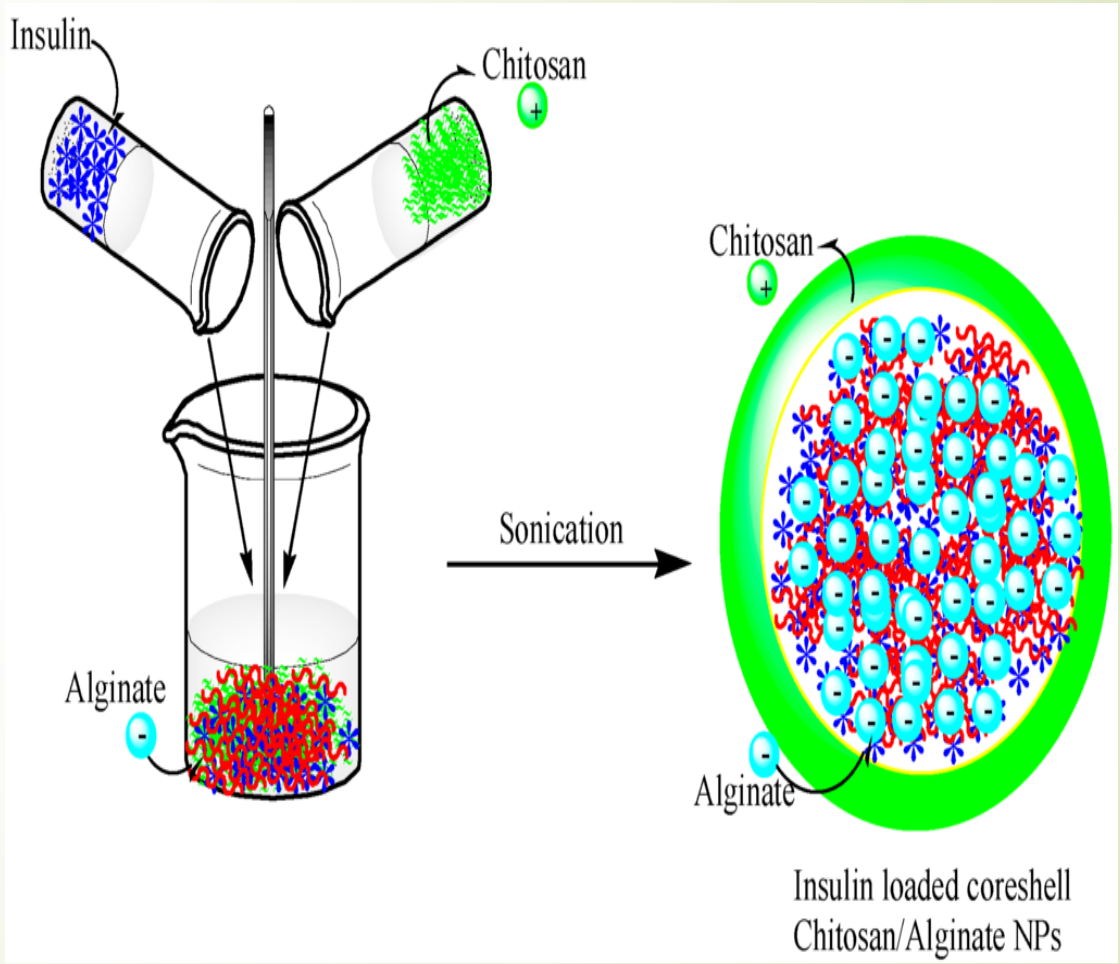
Biomaterial

Discussion

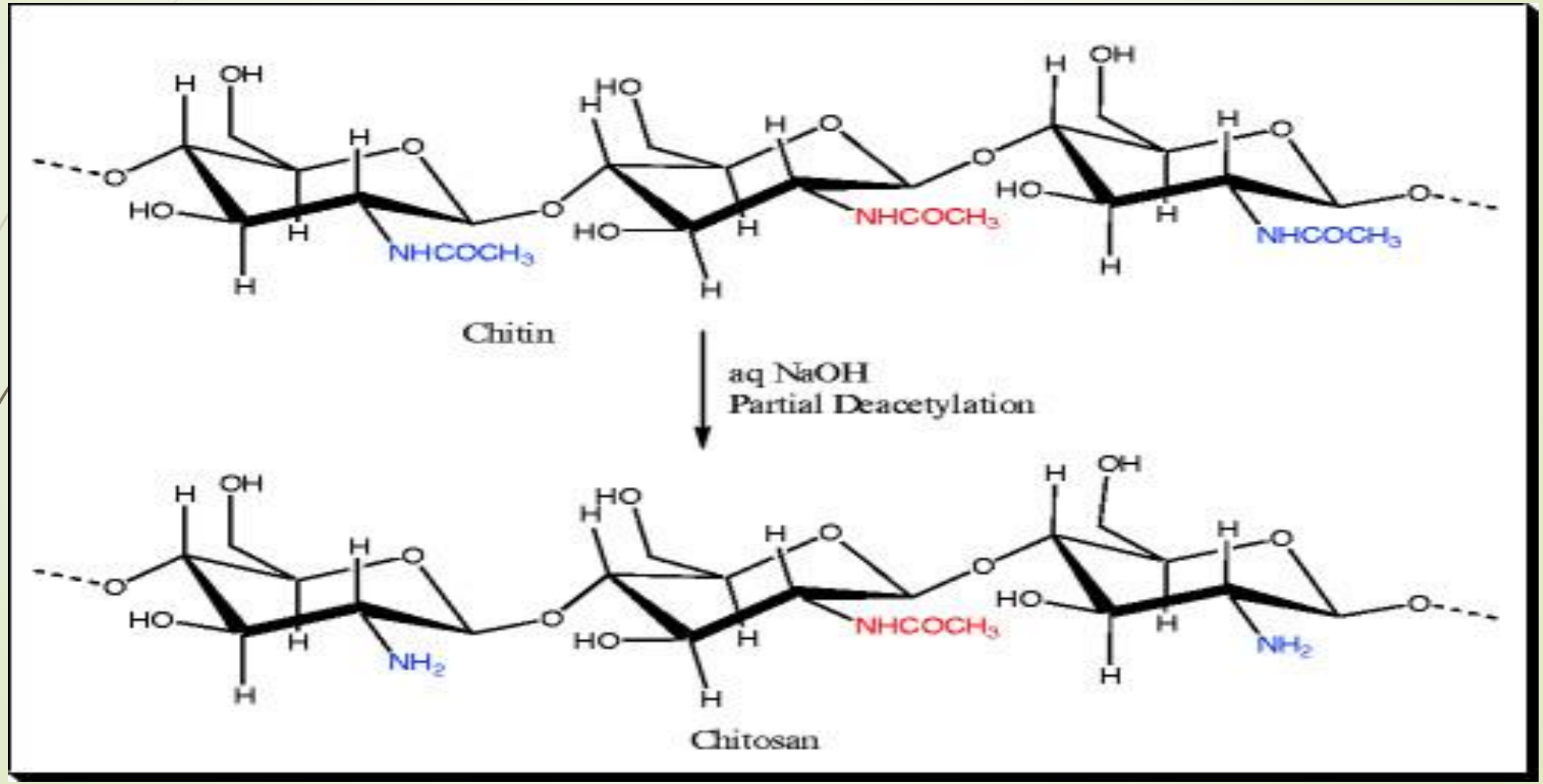
Chitosan

Advantage

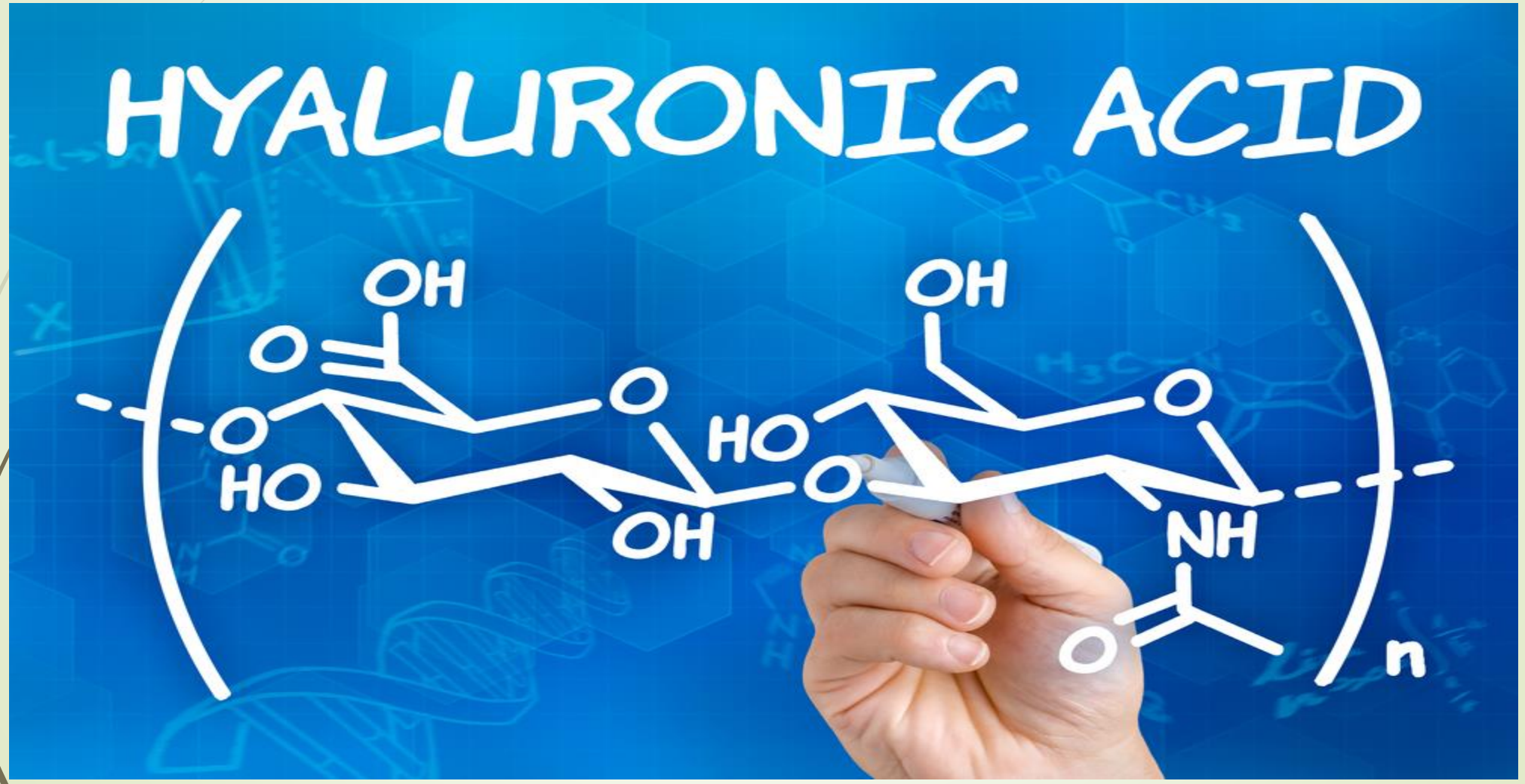
- natural bioadhesive(1)
- biocompatible
- is being used as wound covering
- Drug delivery
- Tissue engineering scaffolds



Discussion



Discussion

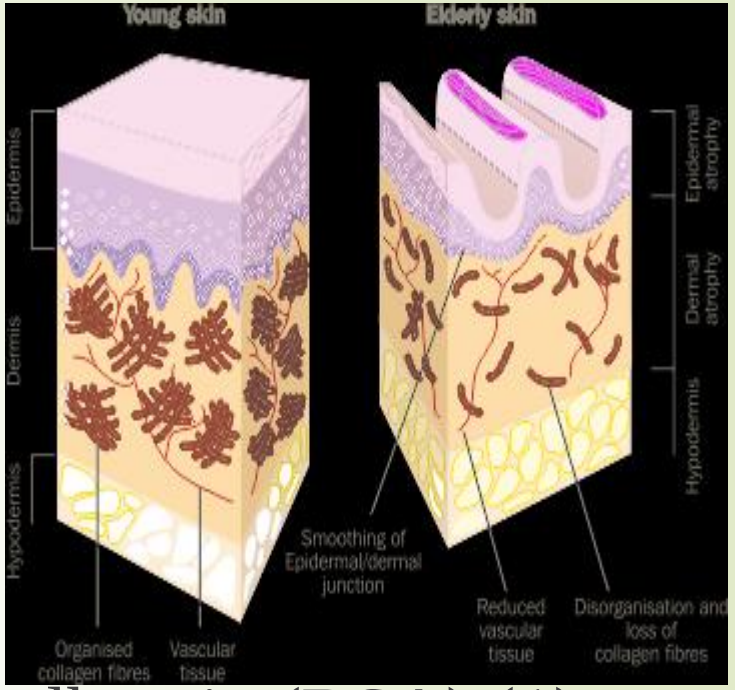


Discussion

Biomaterial

Discussion

collagen



Advantage

- most widely used for medical applications(1)
- intended for controlled release of bovine serum albumin (BSA) (1)
- stimulate the migration cells
- Proliferation cells(14)
- major protein in ECM(14)

Discussion

Collagen…

Disadvantage

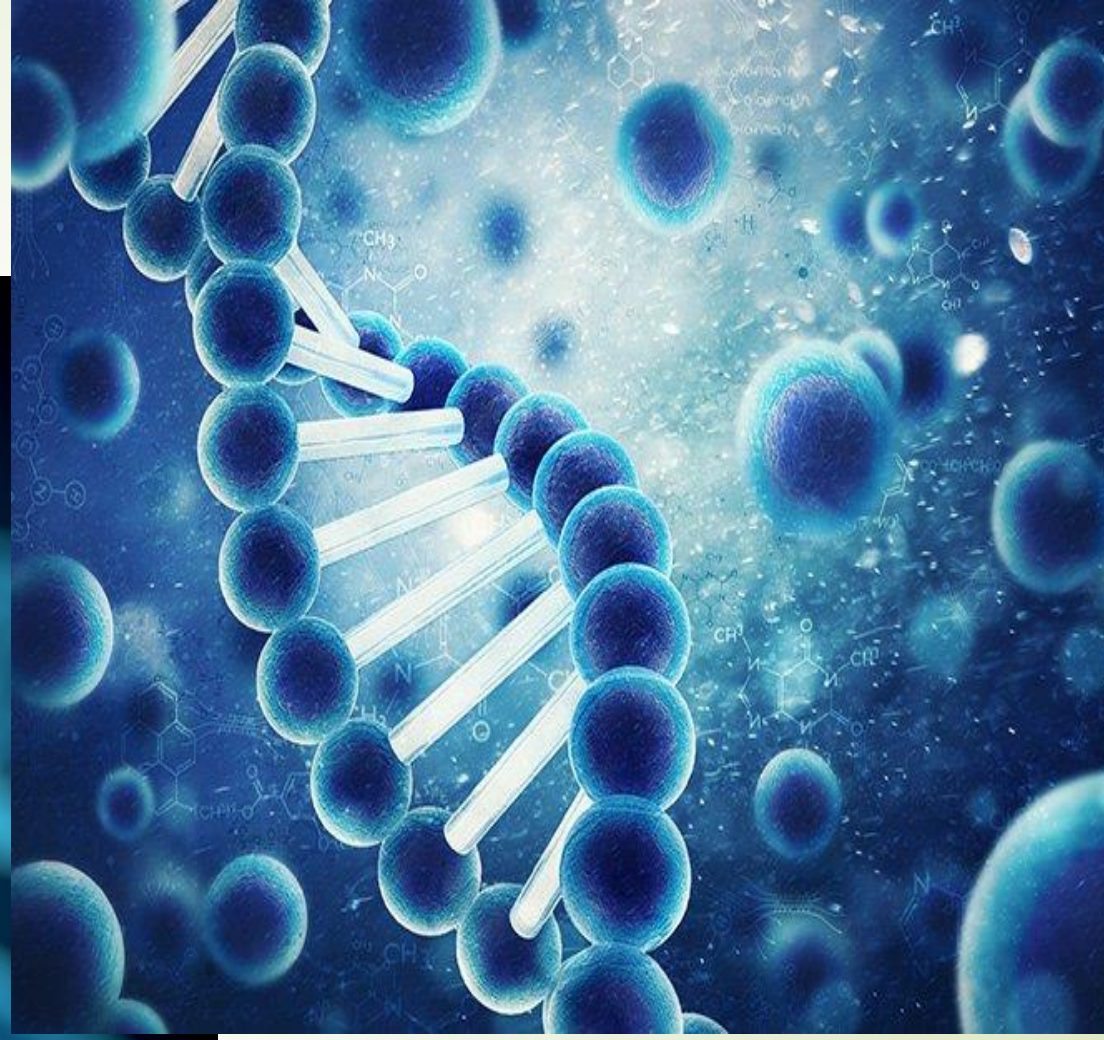
- poor mechanical properties
- unstable
- dissolve in water (1)

Discussion

gelatin

- Gelly in water
- Cartridge capsule
- Drug delivery
- Tissue engineering scaffolds

Discussion



Discussion

DNA

- as a new material for biomedical applications.(11)
- DNA hydrogels prepared for chemical&physical cross-linkers.

Discussion

DNA…

Advantage

- Natural
- biocompatible
- Biodegradable
- as drug delivery(11)

conclusion

- Despite improvement in resistance to degradation after crosslinking, collagen do not have adequate properties (1)

conclusion

blend of different polymers

- collagen/chitosan ✚ glutaraldehyde ⟶ improve their mechanical properties & stability
- collagen/chitosan ✚ genipin ⟶ ⇩ degradation & swelling
- Collagen/hyaluronic acid/poly capro lactone ✚ EDC/NHS ✚ UV ⟶ wound dressings (1)

conclusion

blend of different polymers…

- Glutaraldehyde/malic acid + collagen → ↓ degradation & growth of L 929 cells (1)
- collagen hydrogels + EDC → resistance to collagenase

conclusion

Electrospun fibers

- ✓ ↓ swelling
- ✓ promoted viability of human dermal fibroblasts
- ✓ actin fiber formation

✓ Suggesting for tissue engineering

conclusion

carboxylic acids

- ✓ crosslink both polysaccharides and proteins
- ✓ biocompatible
- ✓ 2 carboxylic groups can crosslink biopolymer in wet and dry conditions
- ✓ fibers, fils, electrospun crosslinked with citric acid.(1)

conclusion

carboxylic acids…

- ✓ Crosslinked in dry & wet condition
- ✓ Improvement in tensile properties
- ✓ ↑ stability under aqueous condition(1)

conclusion

carboxylic acids…

- ✓ Improvement in properties
- ✓ Promote the attachment
- ✓ Proliferation of cells

References

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- 11-Development and characterization of tripolymeric and bipolymeric composite films using glyoxal as a potent crosslinker for biomedical application
- 12-Cisplatin crosslinked pH-sensitive nanoparticles for efficient delivery of doxorubicin
- 13-Preparation and characterization of silk fibroin/collagen sponge modified by chemical cross-linking

THANK YOU

AND THIS

IS END OF MY

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